REMARKS

Claims 1-7 are pending in this application. Claims 5-7 have been withdrawn from consideration. Claims 2-4 have been amended, claims 8-14 have been added, and claim 1 has been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the cancelled subject matter in future applications.

Claims 2-4 have been amended to recite "beagle dog" or "beagle CYP1A2 gene." Support for the amendments can be found throughout the specification, for example, at pages 28-43, in the Examples. Claim 2 has been further amended to recite "determining the CYP1A2 genotype at the base corresponding to a base at position 1117 of the beagle CYP1A2 gene, and determining whether the beagle dog is an extensive metabolizer or a poor metabolizer according to the CYP1A2 genotype." Support for the amendment can be found in the specification, for example, on page 12, at [0018]. Claim 3 has been amended to recite "selecting a beagle dog that is an extensive metabolizer or a beagle that is a poor metabolizer." Support for the amendment can also be found in the specification, for example, on page 12, at [0018], and on page 26, at [0046]. Claim 4 has been amended to recite "assaying a pharmacological effect and/or toxicity of the test drug." Support for the amendment can be found throughout the specification, for example, on page 25, at [0044], and on page 26, at [0046]. Likewise, new claims 8-14 are supported by the specification, for example, on page 12, at [0018]; on page 25, at [0044]; and on page 26, at [0046]. Thus, the amendments and new claims are fully supported by the specification.

Applicants have also amended paragraph [0011] of the specification to correct typographical errors. The amendments add no new matter.

Applicants address below each issue raised in the Office Action of April 26, 2007.

Priority and Drawings

Applicants note with appreciation the acknowledgement of priority and the acceptance of the drawings.

Information Disclosure Statement

The Office noted a listing of references in the specification and that it is not a proper information disclosure statement. Applicants will address the issue in the near future.

Claim Rejections

I. Rejection of claims 1-4 Under 35 U.S.C. § 112, ¶ 1 - Written Description

Claims 1-4 were rejected under 35 U.S.C. 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Office contends that "[g]iven the broad definition in the specification for a base corresponding to 'a base at position 1179 of the nucleotide sequence of SEQ ID NO: 22' the claims encompass mutations and polymorphisms not particularly taught in the instant specification." (Office Action at p. 5). The Office asserts that "the specification appears to suggest that any polymorphism within any CYP1A2 gene would be encompassed by the claims." (*Id.*). The Office further argues that "[s]ince the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a base at position 1179 of the nucleotide sequence of SEQ ID NO:22 is insufficient to teach any base corresponding to a base at position 1117 of any CYP1A2 gene." (Office Action at pages 5-6). Therefore, the Office alleges that "Applicants have not adequately disclosed the

relevant identifying characteristics of a representative number of species within the claimed genus."

In addition, the Office argues that "[t]here is no description of the mutational sites that exist in nature and there is no description of how the structure of CYP1A2 relates to the structure of any strictly neutral alleles." (Office Action at p. 6). The Office further contends that "[t]he specification provides no correlation between structure of polymorphisms and the function of such polymorphisms" and that "a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim." (*Id.*).

Applicants respectfully disagree. The claims, as amended, now recite "beagle dog" and "beagle CYP1A2 gene" and therefore, do not encompass "any CYP1A2 gene." Additionally, contrary to the Office's contention that the specification fails to disclose a representative number of species within the genus, the specification does disclose CYP1A2 sequences of beagle dogs other than SEQ ID NO:22. For example, the specification discloses that:

> . . . the full nucleotide sequence of CYP1A2 cDNA in the EM-type beagle A used in Example 1 was determined as the nucleotide sequence of SEQ ID NO: 22 having the open reading frame (ORF) of nucleotides 63-1601.
>
> Further, full nucleotide sequences of CYP1A2 cDNA in nine EM-type beagles were determined. In the beagle A, bases at positions 1305, 1361, 1365, and 1615 of the nucleotide sequence of SEQ ID NO: 22 were heterogeneously C/G, C/T, G/A, and C/T, respectively. In contrast, the corresponding bases in the other beagles were C, C, G, and C, respectively.

[0065] at p. 34. Thus, the specification does teach a sufficient number of species of the beagle CYP1A2.

Moreover, Applicants disagree that "the specification appears to suggest that any polymorphism within any CYP1A2 gene would be encompassed by the claims." The specification explicitly teaches that a single nucleotide polymorphism (SNP) comprising a substitution of C to T at a base corresponding to a base at position 1117 of a CYP1A2 gene changes an arginine at position 373 of the CYP1A2 protein to a stop codon, resulting in a lack of expression of the CYP1A2 gene and poor drug metabolism:

> In the present invention, the present inventors found an SNP in which a base corresponding to a base at position 1117 of a canine CYP1A2 gene (i.e., at position 87 of exon 4) is substituted from C to T. According to the SNP, a codon encoding arginine (Arg) at position 373 of CYP1A2 changes to a stop codon. As a result, CYP1A2 is not expressed in a dog having a T/T genotype, and thus it is predicted that concentrations of drugs metabolized by CYP1A2 in plasma may become extremely high in comparison with a dog having a C/C genotype or a C/T genotype. As described in Examples, the prediction has been proved from internal dynamics of a phosphodiesterase IV inhibitor, Compound A . . .
>
> As clarified in the present invention, the canine CYP1A2 sometimes contains the stop-codon-causing SNP at position 1117 (i.e., at position 87 of exon 4), and approximately 15% of the dogs have the SNP homogenously. As shown in experiments with Compound A, the SNP is a major factor for individual differences in internal dynamics of drugs metabolized by CYP1A2 in a dog . . .

Pages 10-11 at [0015]-[0016].

Therefore, the specification does teach a structure function relationship between the SNP at position 1117 and drug metabolism. Specifically, a homozygous stop codon at position 1117 in the CYP1A2 gene correlates with poor drug metabolism while the C/C genotype or a C/T genotype correlates with extensive drug metabolism. In addition, as discussed in more detail below under the enablement section, the base A at position 1117 would encode the amino acid

arginine as in the wild type CYP1A2 protein. Therefore, a beagle dog with such a polymorphism would be expected to extensively metabolize a drug. Also discussed under the enablement section, the base G at position 1117 does not generate a stop codon but encodes the amino acid glycine. Therefore, one skilled in the art would expect that a beagle dog with the base G at position 1117 would also be an EM dog.

In sum, the specification does provide sufficient written description for determining whether a beagle dog is an extensive metabolizer or a poor metabolizer by analyzing a base corresponding to a base at position 1117 of a beagle CYP1A2 gene, and determining the CYP1A2 genotype at the base corresponding to a base at position 1117 of the beagle CYP1A2 gene. Accordingly, Applicants respectfully request withdrawal of the rejection.

II. Rejection of claims 1-4 Under 35 U.S.C. § 112, ¶ 1 - Enablement

Claims 1-4 were rejected under 35 U.S.C. § 112, first paragraph, because "the specification, while being enabling for a method of sequencing the known Dah2 gene from beagles, does not reasonably provide enablement for a method for detecting a canine CYP1A2 genetic polymorphism in any canine and associating the polymorphism with 'extensive' and 'poor' metabolizers." (Office Action at p. 7).

The Office asserts that the "invention is in a class of invention which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology.'" (*Id.*). The Office provided two post-filing date references, Mise (*Pharmacogenetics*, 14:769-773, Nov. 2004) and Tacher et al. (*J. of Heredity* 96:812-816, 2005), to support its assertion. The Office contends that Mise "teaches that PM dogs were homozygote of the mutant allele and EM dogs were homozygote or heterozygote of the wild-type allele . . . [and] thus illustrates the importance of

heterozygotes and homozygote distinguishments." (Office Action at p. 8). However, the Office does acknowledge that Mise had fully genotyped beagle dogs. (*Id.*). Meanwhile, the Office refers to Tacher et al. to suggest "breed specificity of many mutations." (*Id.*). The Office alleges that "Tacher specifically teaches that the level of polymorphisms was high but some alleles are breed specific or rare in the dog population with some representing the major allele in the breeds concerned (abstract)." (*Id.*). Again, the Office acknowledges that "[t]he post filing date art also analyzed beagles but suggested that [there] are many breeds of dogs other than beagles." (Office Action at p. 9). Because the Office considers the claims to be "broadly drawn to any canine subject" and "the specification analyzed only beagles," the Office argues that "[t]he skilled artisan would be required to perform further unpredictable and undue experimentation to determine whether the results obtained in the instant specification would extend across additional breeds." (*Id.*).

Furthermore, while acknowledging that the specification "teaches the SNP at position 1117 of a canine CYP1A2 gene (i.e., at position 87 of exon 4) is substituted from C to T," the Office alleges that "[a] base corresponding to 'a base at position 1179 of the nucleotide sequence of SEQ ID NO: 22' is not particularly limited, so long as it is a base at position 1117 of a canine CYP1A2 gene. Namely, it is not necessary for each flanking sequence at either the 5' or 3' side of the 1117th base to accord exactly with that of SEQ ID NO: 22." (Office Action at p. 9). Moreover, the Office contends that "the claims do not appear to set forth the base associated with metabolization of drugs." (*Id.*). The Office argues that:

> The art teaches the C to T polymorphism is located at position 1179 of SEQ ID NO:22. The poor metabolizers are T/T and the extensive metabolizers are C/C or C/T. Thus, the claims which broadly are drawn to any base sequence do not provide the skilled

> artisan with guidance how to determine which dogs are extensive metabolizers based on the presence of an A or G, for example."

(Office Action at p. 9-10).

Thus, the Office concludes that "in a highly unpredictable art where the art teaches the difficulties of associating polymorphisms with phenotypes, the broad scope of the claims would require additional, unpredictable experimentation." (Office Action at p. 10). Applicants respectfully disagree.

As discussed above, the claims, as amended, now recite "beagle dog" and "beagle CYP1A2 gene." Therefore, the claims do not encompass "detecting a canine CYP1A2 genetic polymorphism in any canine." The instant specification discloses "an SNP in which a base at position 1117 of a beagle CYP1A2 gene . . . is substituted from C to T and an amino acid position 373 is changed from arginine to a stop codon" (page 34, 4th full paragraph). The specification further discloses that:

> When the base is a **C/C genotype or a C/T genotype**, it can be judged that the **dog is EM** [extensive metabolizer]. When the base is a **T/T genotype, it can be judged that the dog is PM** [poor metabolizer].

Page 12, first full paragraph (emphasis added). The specification explains the C/C, C/T, and T/T genotypes as follows:

> "C/C" means a subject homogenously carrying the C allele in which the base at position of the CYP1A2 gene (i.e., at position 87 of exon 4) is C, "T/T" means a subject homogeneously carrying the T allele in which the base is T, and "C/T" means a subject heterogeneously carrying both alleles.

Page 39, 4th full paragraph. Therefore, the specification teaches that PM dogs are homozygous for the T allele and EM dogs are heterozygotes or homozygotes for the wild-type allele. This genotype and phenotype relationship was confirmed in beagle dogs (page 43, first paragraph) ("the EM-type beagles included two subjects of the C/C genotype and three subjects of the C/T genotype, and the PM-type beagles included five subjects of the T/T genotype."). Thus, the specification fully enables the determination of whether a beagle dog is an extensive metabolizer or a poor metabolizer by analyzing a base corresponding to a base at position 1117 of a beagle CYP1A2 gene and determining its genotype.

The Office's post-filing date reference to Mise et al. supports the enablement of the instant invention. As taught by the instant specification, Mise et al. genotyped the beagle CYP1A2 gene, and observed that "PM [poor metabolizer] dogs . . . had a nonsense mutation (C1117) that induced a premature termination in position 373" and that "PM dogs were homozygote of the mutant allele (m/m), and EM [extensive metabolizer] dogs were homozygote or heterozygote of the wild-type allele . . . ." (Mise et al., p. 771, col. 2, 2nd and 3rd paragraphs). On the other hand, the post-filing date reference of Tacher et al. appears to be irrelevant to the claimed invention because Tacher et al. discusses the olfactory receptor gene and teaches nothing about the CYP1A2 gene.

To the Office's allegation that "it is not necessary for each flanking sequence at either the 5' or 3' side of the 1117th base to accord exactly with that of SEQ ID NO: 22," Applicants refer the Office to the argument set forth under the written description requirement. There, Applicants provided support for and exemplification of beagle CYP1A2 genes, including SEQ ID NO: 22 and sequences other than SEQ ID NO: 22.

Finally, the Office appears to suggest that the specification teaches the phenotypes of dogs having a C/C, C/T, and T/T genotype at the base corresponding to the 1117th base of a CYP1A2 gene, but not when the base corresponding to the 1117th base corresponds to A or G. However, substitution of A at position 1117 produces codon AGA, which encodes the amino acid arginine, as in the wild-type protein. Thus, one skilled in the art would expect a dog with a substitution of A at position 1117 to be an EM dog. On the other hand, although substitution of G at position 1117 produces codon GGA, which produces the amino acid glycine, it does not create a stop codon in the CYP1A2 gene that is characteristic of a PM dog. Therefore, one skilled in the art could reasonably expect a dog with a substitution of G at position 1117 would be an EM dog.

Accordingly, Applicants believe that the claimed invention is fully enabled and respectfully request withdrawal of the rejection.

III. Rejection of Claims 1-4 under 35 U.S.C. § 112, ¶ 2

(1) Claims 1-4 were rejected as being indefinite for the recitation of "at position 1179 of the nucleotide sequence of SEQ ID NO:22" because it is allegedly unclear whether the polymorphism is at base position 1117 or position 1179. Applicants have deleted the recitation of "at position 1179 of the nucleotide sequence of SEQ ID NO:22" without prejudice or disclaimer, and the claims now recite only "a base corresponding to a base at position 1117 of a beagle CYP1A2 gene." "Position 1117" of a beagle CYP1A2 gene is relative to the position of the start codon of the beagle CYP1A2 gene, as supported by the specification. First, the specification clearly defines "a base corresponding to a base at position 1117 of a beagle

CYP1A2 gene" as "a base corresponding to 'a base at position 1179 of the nucleotide sequence of SEQ ID NO: 22' in a canine CYP1A2 gene . . . As canine CYP1A2 genes, there are various nucleotide sequences, for example, . . . a nucleotide sequence consisting of nucleotides 63-1601 of SEQ ID NO: 22 . . . ." (Paragraph bridging pages 11-12). Second, the specification also clearly teaches that the "full nucleotide sequence of CYP1A2 cDNA in the EM-type beagle A' corresponded to "the open reading frame (ORF) of nucleotides 63-1601" of SEQ ID NO: 22 (page 34, 2nd full paragraph). Thus, it is clear that SEQ ID NO: 22 includes 62 nucleotides N-terminal to the start codon of the beagle CYP1A2 gene, and that "position 1117" of a beagle CYP1A2 gene is calculated by subtracting 62 nucleotides from position 1179 of SEQ ID NO: 22. Accordingly, Applicants respectfully request withdrawal of the rejection.

(2) Claims 2-4 were rejected as being indefinite for the recitation of "poor metabolizer" or "extensive metabolizer" because the terms "poor" and "extensive" are allegedly relative terms that render the claims indefinite. The Office alleges that the terms "poor" and "extensive" are not defined by the claim, that the specification does not provide a standard for ascertaining the requisite degree, and that one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicants respectfully disagree.

The phenotypic categorization of subjects into "poor metabolizers" and "extensive metabolizers" is well-known in the art. For example, the beagle dogs in Paulson et al. (*Drug, Metabolism, and Disposition* 27:1133-1142, 1999) (copy enclosed) "with a 24-h plasma celecoxib concentration below the limit of detection of the assay . . . were EMs of celecoxib and dogs with a 24-h plasma celecoxib concentration above the limit of detection of the assay were PMs of celecoxib" (page 1134, col. 2d, first paragraph). Similarly, Wedlund et al. (*J.*

Pharmacology and Experimental Therapeutics 234:662-669, 1985) (copy enclosed), categorized individuals into extensive metabolizers (EM), poor metabolizers (PM), and intermediate metabolizers (IM) of the drug mephentoin (*see* page 663, col. 1, 2nd full paragraph, and Table 1). Mise et al., the post-filing date referenced cited by the Office and discussed above, also showed that "dogs can be phenotyped for AC-3933 hydroxylation based on plasma concentration ratio of SX-5745 (AC-3933 hydroxylated metabolite) to AC-3933 3 h after oral administration of AC-3933" (page 770, col. 1, 4th paragraph). Thus, the terms "poor metabolizer" and "extensive metabolizer" are well-known in the art and one of ordinary skill in the art would know how to phenotype subjects into PM and EM.

In addition, the specification does provide exemplary, but not limiting, parameters for phenotyping beagle dogs into PMs and EMs:

> As to the pharmacokinetic parameters in the unreacted compound, Cmax of type II was 7.5 times that of type I, and AUCinf of type II was 9.7 times that of type I. From the results, it was concluded that type I was type EM and that type II was type PM.

Page 42, first paragraph.

Thus, the instant disclosure, together with the knowledge of one of ordinary skill in the art, makes clear what is meant by "poor metabolizer" and "extensive metabolizer." Accordingly, Applicants respectfully request withdrawal of the rejection.

(3) Claims 2-4 were rejected as being indefinite because it is allegedly unclear what the claims require. The Office alleges that claim 2 "is drawn to a method for determining which dog is an extensive metabolizer or a poor metabolizer but the final process step in the method is determining a base sequence . . . Thus it is unclear whether the method is for determining which

dogs are extensive versus poor metabolizers or merely detecting a base at position 1117." (Office Action at p. 12). The Office also argues that "[c]laims 3 and 4 are indefinite because the preamble and the final process step do not clearly set for[th] the completion of the method." (*Id.*). Applicants respectfully disagree.

Claim 2, as amended, recites the step of "determining whether the beagle dog is an extensive metabolizer or a poor metabolizer" and therefore makes clear that the claim is not just a method for detecting a base at position 1117. Likewise, claims 3 and 4, as amended, recite the steps of "selecting a beagle dog that is an extensive metabolizer or a beagle dog that is a poor metabolizer" and "assaying a pharmacological effect and/or toxicity of the test drug," respectively. Therefore, withdrawal of the rejection is requested.

IV. Rejection of Claims 1-4 under 35 U.S.C. § 102

Claims 1-4 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Uchida et al. (*Molecular Pharmacology* 38:644-651, 1990). The Office made the rejection because it was unclear what the claimed method actually required, as discussed under the 35 U.S.C. § 112, second paragraph, rejection. The Office indicated that "[i]n the event that the claims only require the active process steps claimed, the following rejection is appropriate. It is noted that the claims are directed to determining a base corresponding to a base at position 1179 of SEQ I D NO:22." (Office Action at p. 12). Specifically, the Office alleges that the "Dah2 sequence of Uchida is 100% identical over the region comprising position 1179 of SEQ ID NO: 22. Thus, Uchida teaches determining the base corresponding to a base at position 1179 of SEQ ID NO: 22." (Office Action at p. 12-13). Applicants respectfully disagree.

Under the discussion of the 35 U.S.C. § 112, second paragraph, rejection, Applicants made clear that claim 2 is not directed to simply determining the base corresponding to a base at position 1179 of SEQ ID NO:22, but requires the step of "determining whether the beagle dog is an extensive metabolizer or a poor metabolizer." Because claims 3 and 4 ultimately depend on claim 2, they also require this step. Uchida et al. does not teach that step. Therefore, Uchida et al. does not anticipate the claims and withdrawal of the rejection is respectfully requested.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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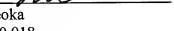
By: 
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